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## **Continuous positive airway pressure alters cranial blood flow and cerebrospinal fluid dynamics at the craniovertebral junction**

Yiallourou, Theresia I ; Schmid Daners, Marianne ; Kurtcuoglu, Vartan ; Haba-Rubio, José ; Heinzer, Raphael ; Fornani, Eleonora ; Santini, Francesco ; Sheffer, Daniel B ; Stergiopoulos, Nikolaos ; Martin, Bryn A

**Abstract:** Purpose: To investigate the impact of continuous positive airway pressure (CPAP) applied by a full-face fitted mask at 15 cmH<sub>2</sub>O on total cerebral blood flow (tCBF), jugular venous flow (tJVF) and cerebrospinal fluid (CSF) flow. Materials and methods: Axial 2D phase-contrast MRI measurements were acquired at the C2–C3 vertebral level for 23 healthy male awake subjects at baseline (without) and with CPAP applied. CSF flow was quantified within the spinal subarachnoid space and tCBF was quantified based on the summation of blood flow within the left and right internal carotid and vertebral arteries. tJVF was quantified based on the summation of blood flow within the left and right jugular veins. Heart rate, transcutaneous carbon dioxide (PtcCO<sub>2</sub>) and oxygen saturation were continuously monitored during the MR protocol. Results: CPAP decreased the pulse amplitude (PtPPA) of tJVF by 21% ( $p = 0.004$ ). CSF stroke volume (SV) and PtPPA also decreased by 20% ( $p = 0.003$ ) and 15% ( $p = 0.005$ ), respectively. Change in tCBF SV and PtPPA was not significant. However, the timing of maximum systolic tCBF occurred significantly earlier under CPAP. CSF flow and tJVF waveforms showed significant spatial and temporal differences in waveform feature points, and spectral analysis revealed a decrease in the first harmonic of tJVF under CPAP ( $p = 0.001$ ). Under CPAP, a 5% decrease in PtcCO<sub>2</sub> ( $p = 0.003$ ) and 9% increase in HR ( $p = 0.006$ ) were measured. However, these HR and PtcCO<sub>2</sub> changes were not correlated with any changes in arterial, venous or CSF flow dynamics. Conclusion: Application of CPAP via a full-fitted mask at 15 cm H<sub>2</sub>O was found to have a significant effect on intracranial venous outflow and spinal CSF flow at the C2 vertebral level in healthy adult-age awake volunteers. CPAP can be used to non-invasively provoke changes in intracranial and CSF flow dynamics.

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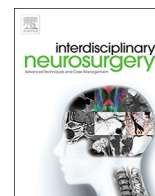
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## Continuous positive airway pressure alters cranial blood flow and cerebrospinal fluid dynamics at the craniovertebral junction



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### ABSTRACT

**Purpose:** To investigate the impact of continuous positive airway pressure (CPAP) applied by a full-face fitted mask at 15 cmH<sub>2</sub>O on total cerebral blood flow (tCBF), jugular venous flow (tJVF) and cerebrospinal fluid (CSF) flow.

**Materials and methods:** Axial 2D phase-contrast MRI measurements were acquired at the C2–C3 vertebral level for 23 healthy male awake subjects at baseline (without) and with CPAP applied. CSF flow was quantified within the spinal subarachnoid space and tCBF was quantified based on the summation of blood flow within the left and right internal carotid and vertebral arteries. tJVF was quantified based on the summation of blood flow within the left and right jugular veins. Heart rate, transcutaneous carbon dioxide (PtcCO<sub>2</sub>) and oxygen saturation were continuously monitored during the MR protocol.

**Results:** CPAP decreased the pulse amplitude (PtPPA) of tJVF by 21% ( $p = 0.004$ ). CSF stroke volume (SV) and PtPPA also decreased by 20% ( $p = 0.003$ ) and 15% ( $p = 0.005$ ), respectively. Change in tCBF SV and PtPPA was not significant. However, the timing of maximum systolic tCBF occurred significantly earlier under CPAP. CSF flow and tJVF waveforms showed significant spatial and temporal differences in waveform feature points, and spectral analysis revealed a decrease in the first harmonic of tJVF under CPAP ( $p = 0.001$ ). Under CPAP, a 5% decrease in PtcCO<sub>2</sub> ( $p = 0.003$ ) and 9% increase in HR ( $p = 0.006$ ) were measured. However, these HR and PtcCO<sub>2</sub> changes were not correlated with any changes in arterial, venous or CSF flow dynamics.

**Conclusion:** Application of CPAP via a full-fitted mask at 15 cm H<sub>2</sub>O was found to have a significant effect on intracranial venous outflow and spinal CSF flow at the C2 vertebral level in healthy adult-age awake volunteers. CPAP can be used to non-invasively provoke changes in intracranial and CSF flow dynamics.

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### 1. Introduction

The coupling of cerebrospinal fluid (CSF) pressure fluctuations and the cardiovascular system has long interested researchers [1–3]. A full

understanding of this coupling is thought to be important to understand the pathophysiology of cerebrovascular disorders such as stroke, interstitial fluid transport within the brain [4,5], and craniospinal disorders such as type I Chiari malformation, syringomyelia and hydrocephalus [6–9]. A number of studies have sought to understand the CSF dynamics in the spinal subarachnoid space (SSS) and its importance for the overall intracranial balance between the arterial, venous, and CSF flow pulsations [10–12]. Researchers have postulated that under normal conditions the healthy SSS may act as a “notch filter” that dampens incoming cerebral blood flow (CBF) pulsations to supply smooth blood flow to the neural tissue [13,14]. In addition, Martins et al. [15] showed that the spinal dural sac is a dynamic structure, readily changing its capacity in response to intra-abdominal pressure fluctuations.

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Non-invasive 2D phase-contrast magnetic resonance imaging (2D PC MRI) enables measurement of the CSF and CBF system fluid flow [16,17] and has also been used to estimate venous flow in the jugular and intracerebral veins as well as the major sinuses [12]. According to the Monro–Kellie doctrine [12], the arterial, venous, CSF and brain tissue compartments co-exist in a state of dynamic equilibrium throughout the cardiac cycle [18–20]. A change in the volume in one component requires a change in the volume in either one or both of the other two compartments. Schmid Daners et al. [21] showed using 2D PC MRI that the coupling of cerebral arterial inflow and CSF dynamics is age and sex dependent. Other studies have focused on the cerebral venous system [20,22]. El Sankari et al. [22] simultaneously compared the venous flow, arterial and CSF flows of patients with multiple sclerosis to age and sex matched healthy adults. Results documented complex and heterogeneous venous drainage pathways and a decrease in CSF flow oscillations.

The interaction between intrathoracic pressure and intracranial pressure (ICP) due to posture [23], abdominal pressure changes [24] and coughing [25] has been reported in the literature. These pressure changes are transmitted from the abdomen into the CSF system through the dural venous sinuses and epidural venous plexus [26]. Published data have shown physiologic variations in the dural venous sinus drainage that can occur either under specific respiratory mechanisms such as Valsava maneuver [27] or with posture changes [28]. Thus, it is possible to manipulate the intrathoracic pressure by a number of non-invasive maneuvers that in turn modify the intracranial system as a whole. One method to non-invasively alter intrathoracic pressure is with the use of continuous positive airway pressure (CPAP), the most widely accepted treatment for sleep apnea. CPAP acts as a pneumatic “splint” by producing a positive pressure, thereby preventing upper airway collapse during sleep.

While CPAP use has become routine, the full physiological effect of its use on CBF, venous flow and CSF dynamics is not fully understood [29,30]. Considering that a rise of the intrathoracic pressure increases the jugular venous pressure, CPAP could have an effect on CBF by reducing the cerebral perfusion pressure [31]. Concomitantly, changes in the blood flow volume due to the increased intrathoracic pressure hinder cerebral venous drainage via the jugular veins [32]. In human volunteers CPAP breathing has been shown to increase lumbar CSF pressure [33] and reduce CSF peak velocity in the aqueduct of Sylvius [34].

In the present study, we hypothesized that acute pressure changes in the chest caused by the application of CPAP would alter intracranial and spinal CSF flow dynamics in the following manner: 1) venous flow dynamics would be noticeably altered and 2) the stroke volume (SV) and pulsation of the spinal CSF would decrease. We tested our hypothesis by applying CPAP at 15 cm H<sub>2</sub>O in 23 healthy male volunteers and measured physiological alterations using a 2D PC MRI protocol to quantify blood flow in the left and right internal carotid arteries (ICAs), left and right vertebral arteries (VAs), left and right jugular veins (JVs) and CSF flow at the C2–C3 level of the cervical spinal canal with CPAP applied. Baseline measurements without CPAP applied followed the initial recording with the CPAP using identical imaging protocols. Using these measurements the influence of CPAP on total cerebral blood flow (tCBF), total jugular venous (tJVF) and spinal CSF flow was assessed in terms of flow based metrics and spectral content of the flow waveforms.

## 2. Materials and methods

### 2.1. Ethics statement

Healthy, young, non-smoking male volunteers, with no history of pulmonary, cardiac, neurological, cerebral disease, spinal trauma or diagnosed sleep apnea, were invited to participate in the study by advertisement at the local university hospital of Lausanne, Centre Hospitalier Universitaire Vaudois (CHUV) and École Polytechnique

Fédérale de Lausanne in Switzerland. The study was carried out in accordance with the Declaration of Helsinki (1989) and was approved by the Swiss Human Research Ethics Committee of Vaud. The MR data acquisition was performed at the Centre d’Imagerie BioMédicale (CIBM) Department of Radiology, CHUV in Lausanne. Before the MR exams, written informed consent was obtained for all volunteers. MR data were anonymized prior to data post-processing.

### 2.2. In vivo 2D PC MR measurements

23 healthy male volunteers, aged  $24 \pm 2.1$  years with a mean body mass index (BMI) of  $22.9 \pm 2.51$  kg/m<sup>2</sup> were scanned on a 3 T MRI scanner (Siemens Magnetom Trio Tim, Siemens, Erlangen, Germany) with a standard 4-channel phased array carotid coil (Magnet Mach NET 4CHN, Siemens A Tim Coil), placed adjacent to the left and right ICAs and a neck coil (Neck matrix, 4CHN, Siemens) with CPAP (S8 AutoSet Spirit™ II, ResMed Inc, Poway, CA) applied at 15 cmH<sub>2</sub>O through a fitted full-face mask MIRAGE QUATTRO® (ResMed®, ResMed Inc, Poway, CA) in a specific order following a structured protocol. The measurements were performed during the afternoon at atmospheric pressure in the MR scanner room with controlled temperature at least two hours after the last meal and caffeinated drink. A medical doctor was present throughout testing. Subjects were awake during the entire MRI protocol in the supine position with their necks in a neutral orientation.

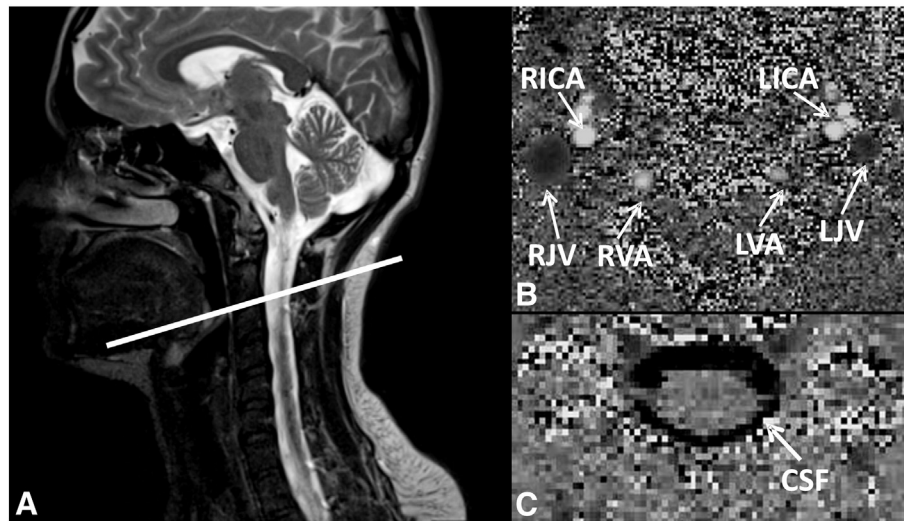
Both anatomy and 2D PC MR images were acquired. A set of T2-weighted turbo spin-echo sagittal images defined the anatomy in the upper cervical spine. Fluid flow acquisition planes, oriented perpendicular to the nominal flow direction, were selected based on a mid-sagittal scan at the C2–C3 subarachnoid space (Fig. 1A). Both left and right ICAs, left and right VAs and left and right JVs were imaged by 2D PCMRI simultaneously within the same slice oriented orthogonal to the spinal cord axis at the C2–C3 cervical level (Fig. 1B). Imaging parameters for the arterial and jugular flow measurements were as follows: 0.7 mm isotropic in-plane resolution, 5 mm slice thickness,  $124 \times 114$  acquisition matrix, 20° flip angle, 814 Hz/Px bandwidth,  $190 \times 112$  field of view (FoV), 59.4% FoV phase, 256 base resolution, 100% phase resolution, 80 cm/s thru-plane velocity encoding (VENC) and TR = 20 ms and TE = 6.5 ms, which resulted in a temporal resolution of 20 ms. The minimum TR available was used to optimize temporal resolution, and the minimum TE available was used to optimize signal-to-noise ratio and to reduce intravoxel phase dispersion. All scans were prospectively triggered with electrocardiographic (ECG) gating. The number of heart phases acquired was adapted to the cardiac frequency and fixed to 35 phases for all the subjects.

CSF flow measurements were performed at the same location as the vascular flow measurements (Fig. 1C) with the imaging parameters identical to those of the vascular flow measurements, except with a VENC of 10 cm/s and 15° flip angle. Overall scan time was 8–10 min with CPAP and 8–10 min without CPAP applied, depending on the heart rate. The entire examination was approximately 45 min.

### 2.3. Physiologic monitoring

Transcutaneous partial pressure of carbon dioxide (PtcCO<sub>2</sub>), oxygen saturation (SaO<sub>2</sub>) and heart rate (HR) were monitored throughout the exam with a ‘Tosca 500’ system (Radiometer Basel AG, Basel, Switzerland) using a sensor applied at the top surface of the foot. MRI measurements under CPAP were obtained first after the PtcCO<sub>2</sub> level return to baseline ( $\pm 2$  mmHg) or at least 15 min of CPAP use. Following the MRI measurements with CPAP, the mask was removed and the same protocol repeated without CPAP to obtain the ‘baseline’ measurements. Following MR examination, all subjects were asked to rate their anxiety level under CPAP from a scale of 0–3 where 0 refers to ‘not at all anxious’, 1 refers to ‘slightly anxious’, 2 refers to ‘moderately anxious’ and 3 refers to ‘highly anxious’.





**Fig. 1.** (A) Sagittal T2-weighted localizer sequence used to select the C2–C3 vertebral level for 2D PC MRI flow quantification. The acquisition plane was selected perpendicular to the flow direction. (B) 2D PC MRI phase mapping at the C2–C3 level used to measure vascular flows, in the left (L) and right (R) internal carotid arteries (ICAs), vertebral arteries (VAs) and jugular veins (JVs), with and without CPAP (VENC = 80 cm/s, black voxels denote caudal directed flow, white voxels denote cranial directed flow). (C) 2D PC MRI measurement of CSF flow at the C2–C3 measurement plane (VENC = 10 cm/s).

#### 2.4. Data processing and analysis

All 2D PC MR images were post-processed with Segment (Standalone version, Medviso AB, Lund, Sweden) by one operator blinded to subject status. For each scan, flow was determined with an adaptive region of interest (ROI) selection using manual segmentation based on the instantaneous lumen area. Images were visually inspected for adequate signal to noise at the ROI. Datasets presenting major artifacts or too low signal levels were excluded from the subsequent analyses. Aliasing correction and eddy current compensation were performed automatically by the “unwrap” and “eddy current” function of the Phantom experiment method (GE method) [35] procedures in Segment. The ICAs, VAs and JVs were segmented frame by frame in order to account for the temporal change in their cross-section due to the blood pulsation. The cervical SSS was segmented in single-image frames since its cross-sectional area did not vary with time. The ROI of SSS was best outlined in early systole, when the contrast between CSF and spinal cord was at its maximum.

Data visualization and post-processing were performed using image processing software within MATLAB R2010b (The Mathworks Inc., Natick, MA, USA). Flow waveforms were obtained from the recorded velocity for each voxel from the PC MR images and then integrated over the area of each ROI. The process involved integration of the velocity over the manually segmented cross-sectional area for an entire cardiac cycle:  $Q(t) = \sum A_{\text{voxel}}[V_{\text{voxel}}(t)]$ , where  $A_{\text{voxel}}$  is the area of the one MRI voxel,  $V_{\text{voxel}}$  is the velocity of the corresponding voxel, and  $Q(t)$  is the voxel summation of the flow for each voxel of interest [17].

The tCBF into the cranial space was calculated by summing the blood flow rates of the left and right ICAs and left and right VAs:  $tCBF = Q(t)_{ICA} + Q(t)_{VA}$ , where  $Q(t)_{ICA}$  and  $Q(t)_{VA}$  are calculated as the sum of the left and right vessel measurements (i.e.,  $Q_{ICA} = Q(t)_{ICA\text{left}} + Q(t)_{ICA\text{right}}$  and  $Q_{VA} = Q(t)_{VA\text{left}} + Q(t)_{VA\text{right}}$ ). Estimation of the tJVF was obtained by the summation of the flow rates through the left and right JVs:  $tJVF = Q(t)_{JV\text{left}} + Q(t)_{JV\text{right}}$ . CSF flow waveform was offset so the net CSF flow per cycle was zero since the net flow in the SSS is known to be nearly zero [36].

The stroke volume (SV) (mL/cardiac cycle) was also determined for both the vascular and the spinal CSF compartments using the trapezoidal rule by computing volume changes for each time increment, which correspond to the area under the waveform curve of the flow difference into and out of the ROI.

For the frequency and flow rate analysis, the data were temporally and spatially normalized according to Schmid Daners et al. [21]. The length of the cardiac cycle of the subjects with CPAP and during the baseline measurements was  $0.94 \pm 0.17$  s and  $1.0 \pm 0.16$  s, respectively. Therefore, the data were temporally normalized to 1 s and resampled with a time interval of 10 ms. The normalized cardiac cycle allows for comparison of frequency components (expressed in Hertz (Hz)) obtained via discrete Fourier transformation. The frequencies were considered up to the noise level of each compartment, which was evaluated with the standard deviation of the respective compartment signals over all volunteers. The frequency components below one-fifth standard deviation were considered as noise [21]. The zero frequency was not taken into account, because it does not correspond to the net flow due to the spatial normalization. The spinal CSF flow and the tJVF were spatially normalized by the average flow rate over the entire measurement length and the tCBF over the systole only. In general, the spatial normalization aimed at accentuating the flow characteristics.

#### 2.5. Statistical analysis

Statistical analysis was conducted with Minitab 16 (State College, PA) and IBM SPSS Statistics 19 (SPSS Inc., Chicago, IL, US). A Mann–Whitney U test was performed when the variances between groups were not equal. Multivariate analysis of covariance (MANCOVA) was performed to investigate the combined effects of the independent group of variables (height, weight, BMI and age) on each of the calculated dependent variables. Non-normally distributed data were logarithmically transformed before analysis. Frequencies of normalized flow rates that were recorded with CPAP and during the baseline measurements were evaluated using repeated measures analysis of variance (ANOVA) with Greenhouse–Geisser correction to compensate for non-sphericity. The ANOVA was performed within both groups and between the data of the recordings with CPAP and baseline measurements. Individual frequency components were compared with a Mann–Whitney U test. Correlations were calculated with Spearman’s rho. Differences were considered significant at p-value < 0.05.

### 3. Results

All results are presented as mean  $\pm$  standard deviation (SD) for the number of volunteers (n) whose measurements were taken into

account (see Tables 1 and 2). Results were analyzed in terms of average flow, systolic and diastolic peak flow, peak-to-peak pulse amplitude (PtPPA), area and SV of both the vascular and CSF components. Characteristics of the waveforms of the tCBF, tJVF, and spinal CSF flow are described with respect to their feature points and frequency content.

### 3.1. Physiological metrics

Under CPAP, a 5% decrease in PtcCO<sub>2</sub> ( $p = 0.003$ ) and 9% increase in HR ( $p = 0.006$ ) were measured (Table 1). The changes in both HR and PtcCO<sub>2</sub> were not correlated with any of the changes observed in the arterial, venous and CSF flow dynamics. In terms of the anxiety level, the results showed that 70% of the subjects tolerated the CPAP well, reporting “slight anxiety” with a mean value of  $0.35 \pm 0.49$  in the anxiety index. Anxiety was not correlated with any of the independent variables (height, weight, age, BMI). MANCOVA analysis showed that the independent group of variables (weight, height, age and BMI) had no significant effect on the PtPPA and the SV of the tCBF, the tJVF and the CSF flow. A significant effect was observed on HR change by the independent group ( $p = 0.03$ ).

### 3.2. MR-based area and flow metrics

The area of tCBF that corresponds to the sum of areas of left and right ICA and VA decreased significantly under CPAP ( $3 \pm 1 \text{ mm}^2$ ,  $p = 0.015$ ). All other changes in arterial flow-based metrics under CPAP were insignificant (Table 2 and Fig. 2A). Diastolic peak tJVF increased under CPAP by 40% ( $89 \pm 67 \text{ mL/min}$ ,  $<0.001$ ). The PtPPA of tJVF decreased by  $108 \text{ mL} \pm 30 \text{ mL}$  ( $p = 0.004$ ). A significant increase in the total area of JVs (sum of the areas of left and right JV) was observed ( $18 \pm 9 \text{ mm}^2$ ,  $p < 0.001$ ). Volumetric venous and CSF flow rates are depicted in Fig. 2B and Fig. 2C. CSF SV and PtPPA decreased by 20% ( $-0.13 \pm 0.09 \text{ mL}$ ,  $p = 0.003$ ) and 15% ( $-52 \pm 26 \text{ mL/min}$ ,  $p = 0.005$ ), respectively (Table 2). SSS area did not change under CPAP.

### 3.3. Waveform characteristics

Differences of the waveform characteristics between the baseline measurements and with CPAP were analyzed using repeated measures ANOVA. The amplitude of the normalized tCBF ( $p = 0.004$ ) and the temporal locations of the tJVF ( $p = 0.004$ ) as well as the spinal CSF flow ( $p = 0.034$ ) showed that these parameters were significantly different under the presence of CPAP compared to the baseline measurements (Fig. 3). The Mann–Whitney U test of the feature points (Table 3) of the three compartments found the following significant differences: In the tJVF (Fig. 3B), feature points v2 and v3 of the measurements with CPAP occurred significantly earlier in the cardiac cycle, as do s3 and s4 of the spinal CSF flow (Fig. 3C). In contrast, the timing of the systolic maximum (a2) of the tCBF was delayed with CPAP application (Fig. 3A). Additionally, v4 of tJVF, s1, s3 and s4 feature points of the spinal CSF flow were found to have significant amplitude differences between the two groups with CPAP and baseline measurements. The corresponding p-values are listed in Table 3. Several feature points of the normalized flow rates were significantly correlated with the HR: in particular, for the case of tCBF (Fig. 3A), the timing of the aortic valve closure ( $r = -0.588$  and  $p < 0.001$ ) and diastolic maximum

( $r = -0.346$  and  $p = 0.041$ ), for the case of the tJVF (Fig. 3B), the amplitude of v1 ( $r = -0.433$  and  $p = 0.015$ ) and timing of v3 ( $r = -0.453$  and  $p = 0.011$ ) and v4 ( $r = -0.456$  and  $p = 0.008$ ) and lastly, for the case of the spinal CSF flow (Fig. 3C), the amplitude of s1 ( $r = 0.306$  and  $p = 0.041$ ), the timing of s3 ( $r = -0.426$  and  $p = 0.004$ ) and s4 ( $r = -0.530$  and  $p < 0.001$ ).

Frequency components of the normalized flow rates with CPAP were juxtaposed to those collected at baseline (Fig. 4). Significant differences in individual frequency components according to the Mann–Whitney U test are marked with curly brackets and the respective p-values are indicated in Fig. 4. Intra- and inter-subjects effect was evaluated by repeated measures ANOVA. The frequency components of the tCBF (Fig. 4A), the tJVF (Fig. 4B) and the CSF flow (Fig. 4C) were significantly different within the groups with  $p = 0.001$ ,  $p < 0.001$  and  $p = 0.001$ , respectively. The differences between the frequency components of the CPAP and those without were only significant in the case of tJVF ( $p = 0.036$ ).

## 4. Discussion

In the present study, we observed the response of vascular and spinal CSF flow dynamics to the application of CPAP at 15 cmH<sub>2</sub>O in healthy awake male subjects using 2D PC MRI flow measurements. Our hypothesis was that CPAP would alter venous flow patterns due to the increase of the intrathoracic pressure and subsequently decrease the SV and pulse amplitude of spinal CSF flow. Our findings showed that CPAP reduced CSF SV and PtPPA by 20% ( $p = 0.003$ ) and 15% ( $p = 0.005$ ), respectively. In addition, tJVF PtPPA decreased by 21% ( $p = 0.004$ ). tCBF based metrics were not altered by CPAP. Additionally, the normalized tJVF and CSF flow waveforms showed significant spatial and temporal differences with respect to their feature points.

### 4.1. Comparison of results to previous studies

In the past, various studies have employed both transcranial Doppler ultrasound and 2D PC MRI measurements to estimate the effect of CPAP on cerebral and CSF hydrodynamics with conflicting results. In previous work by our group [30], we used Duplex color ultrasound to assess the change in tCBF under CPAP at 15 cmH<sub>2</sub>O in healthy volunteers. Results showed a significant reduction in the tCBF likely related to hypocapnic vasoconstriction. Kolbitsch et al. [34] found that systolic CSF velocity at the aqueduct of Sylvius decreased under CPAP. They reasoned that pressure transmission from the thorax to the craniospinal space increased the spinal CSF pressure, which resulted in an increase of the outflow resistance against the systolic CSF moving into the SSS thereby decreasing the CSF pulsation at the aqueduct. In a subsequent study Kolbitsch et al. [37] documented a significant decrease in the regional CBF volume with the presence of CPAP at 12 cmH<sub>2</sub>O using contrast-enhanced MRI measurements.

It is well accepted that PtcCO<sub>2</sub> impacts the muscular regulation of the vessel wall, with hypercapnia leading to vasodilatation and hypocapnia to vasoconstriction. Kolbitsch et al. [41] observed an increase of the systolic CSF velocity in the presence of CPAP due to hypercapnia when compared to normocapnia caused by a decreased outflow resistance for a systolic craniospinal CSF displacement. In a previous study, we also reported a reduction in the tCBF, but this effect appeared to be mediated predominately through the hypocapnic vasoconstriction coinciding with PtcCO<sub>2</sub> level reduction [30]. The tCBF decreases by approximately 1 ml per 100 g per min for each 1 mmHg decrease in PtcCO<sub>2</sub>. However, in the present study, tCBF was not altered under the presence of CPAP, and the reduction in the PtcCO<sub>2</sub> and HR was not significantly correlated with any of the arterial, jugular or spinal CSF flow changes under CPAP. As a result, our present findings support that the observed changes in the tJVF and CSF dynamics are likely mediated by CPAP acting on the lungs.

**Table 1**  
Physiological changes assessed under CPAP usage (values expressed as mean  $\pm$  SD for the 23 volunteers).

	CPAP	Baseline	p-value
SaO <sub>2</sub> (%)	96 $\pm$ 0.8	99 $\pm$ 1	0.223
Heart rate (bpm)	65 $\pm$ 10	61 $\pm$ 8	0.006
PtcCO <sub>2</sub> (mmHg)	36 $\pm$ 5	38 $\pm$ 4	0.003

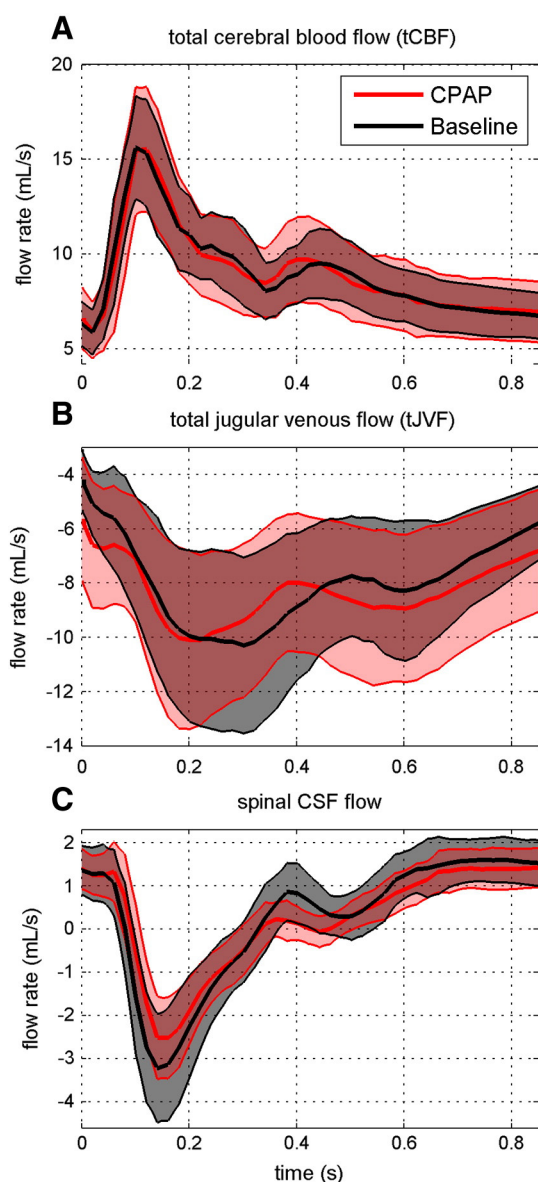
Abbreviations: CPAP: continuous positive airway pressure; PtcCO<sub>2</sub>: Transcutaneous carbon dioxide level; SaO<sub>2</sub>: oxygen saturation.

**Table 2**  
Arterial, vascular and CSF results for the study population with CPAP applied and at baseline.

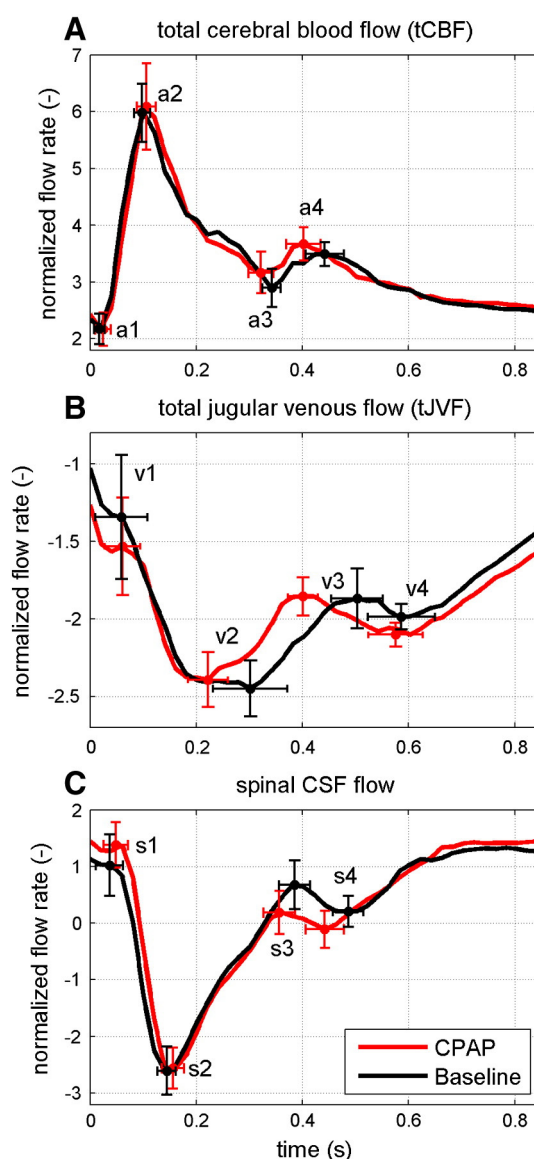
	Total cerebral blood flow (tCBF)			Total jugular venous flow (tJVF)			Spinal CSF flow		
	CPAP	Baseline	p-value	CPAP	Baseline	p-value	CPAP	Baseline	p-value
n	17	18		17	14		22	23	
Average flow (mL/min)	547 ± 119	552 ± 104	N.S.	−529 ± 171	−517 ± 146	N.S.	N/A	N/A	–
Systolic peak flow (mL/min)	940 ± 196	933 ± 167	N.S.	−654 ± 215	−673 ± 195	N.S.	−165 ± 55	−207 ± 78	0.002 ↓
Diastolic peak flow (mL/min)	344 ± 88	338 ± 75	N.S.	−350 ± 149	−261 ± 82	<0.001 ↑	104 ± 27	114 ± 31	N.S.
PtPPA (mL/min)	596 ± 131	595 ± 123	N.S.	−304 ± 127	−412 ± 157	0.004 ↓	−269 ± 79	−321 ± 105	0.005 ↓
Area of the ROI (mm <sup>2</sup> )	64 ± 14	67 ± 13	0.015 ↓	84 ± 32	66 ± 23	<0.001 ↑	115 ± 19	118 ± 23	N.S.
SV (mL/cardiac cycle)	9.1 ± 2.0	9.2 ± 1.7	N.S.	8.8 ± 2.8	8.6 ± 2.4	N.S.	0.49 ± 0.15	0.62 ± 0.25	0.003 ↓

Abbreviations: n: indicates number of volunteers included for the measurement; CPAP: continuous positive airway pressure; CSF: cerebrospinal fluid; PtPPA: peak-to-peak pulse amplitude; SV: stroke volume; N.S.: no significant change (↓ refers to a statistically significant decrease and ↑ refers to a statistically significant increase under CPAP).

Intra-abdominal pressure as well as several modified respiratory conditions such as hyperventilation, Valsava maneuver and jugular vein compression has been shown to have a similar effect on intracranial dynamics as CPAP in the present study [15,24,42]. In particular, elevated intra-abdominal pressure appeared to significantly increase ICP



**Fig. 2.** Volumetric flow rates for the total cerebral blood flow (tCBF) (A), the total jugular venous flow (tJVF) (B) and the spinal CSF flow (C). The results are depicted as a mean (bold line) of the included subjects with CPAP (red) and without (black, baseline) CPAP applied. The shaded area shows the corresponding standard deviation (SD).



**Fig. 3.** Normalized flow rates of the tCBF (A), tJVF (B) and spinal CSF flow (C). The results are depicted as a mean of the included subjects with (red) and without (black, baseline) CPAP. Feature points are marked with the corresponding standard deviation (SD) error bars with respect to timing and flow deviations. Panel A shows the sum of mean (over subjects) normalized flow velocity curves in the left and right ICAs and the left and right VAs that corresponds to the tCBF. Panel B depicts the sum of the mean in the left and right JVs that corresponds to the tJVF. Panel C depicts the mean CSF flow. Positive values correspond to flow in the caudocranial direction. A waveform feature point legend is provided in Table 3 including the p-values evaluated by the Mann–Whitney U test.



**Table 3**

Legend of waveform feature points in the corresponding compartments including statistically significant results.

Feature Point		Mann–Whitney U test (p-value)	
<b>Total Cerebral Blood Flow (tCBF)</b>		temporal	spatial
a1	diastolic minimum	0.035	
a2	systolic maximum		
a3	aortic valve closure		
a4	diastolic maximum		
<b>Total Jugular Venous Flow (tJVF)</b>			
v1	local maximum	0.032	
v2	maximum caudal flow		
v3	local maximum		
v4	local minimum	<0.001	0.003
<b>Spinal CSF Flow</b>			
s1	local maximum cranial flow	<0.001	
s2	maximum caudal flow		
s3	local maximum	0.002	0.004
s4	local minimum	<0.001	0.011

in an anesthetized and ventilated swine and decrease cerebral perfusion pressure which in turn reduced the cerebral venous outflow via the jugular venous system [24]. In addition, Hogan et al. [43] found with the use of MRI that abdominal compression in healthy volunteers significantly decreased CSF volume which was primarily attributed to the displacement of tissue into the vertebral canal through the intravertebral foramina. Researchers conjectured that ICP alterations are compensated by the variable capacity of the spinal dural sac. Notably, myelography has been used to examine the dural sac diameter [15,44] and cord dimensions [45]. Martins et al. [15] concluded that the spinal dural sac can change its capacity in response to prevailing pressure gradients across its walls. Thus, the dural sac acts as a CSF reservoir in response to changes in cerebral blood flow that provides "elasticity" to the CSF system.

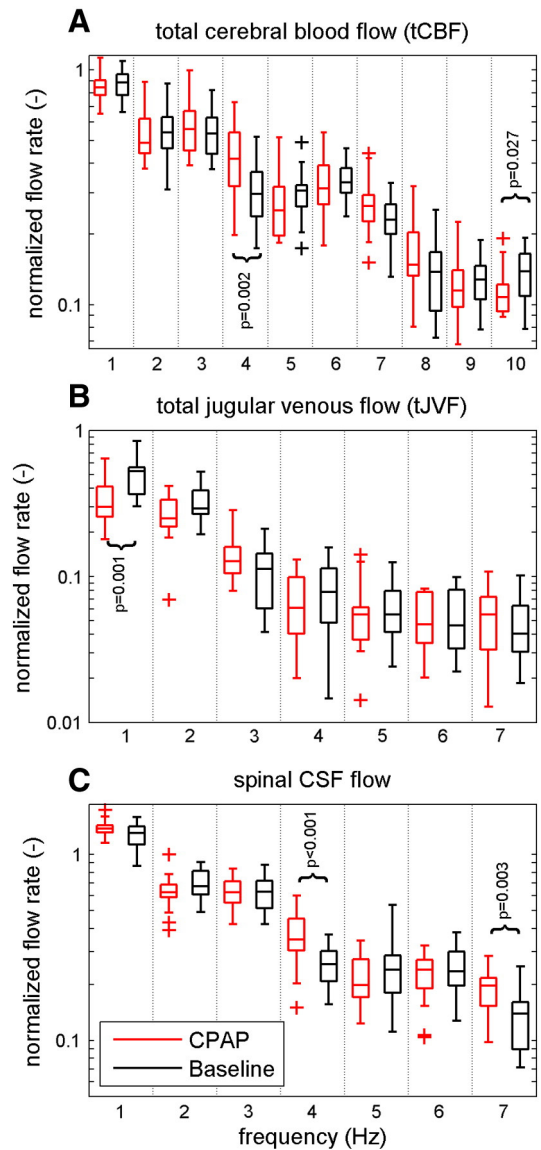
#### 4.2. Physiological mechanism responsible for CBF and CSF alterations

The observed decrease in spinal CSF PtPPA and SV under CPAP is likely due to the impact CPAP had on the timing of tJVF and, to a lesser extent, tCBF pulsations. The physiological mechanism responsible for alterations to vascular and CSF flow dynamics under CPAP is complex. CPAP is accompanied by an increase in intrathoracic pressure, which leads to increased central venous pressure and decreased venous return, causing a dilatation of the jugular veins as reflected by the significant increase in the cross-sectional area of the left and right JVs (see Table 2). However, there was no significant change in the SV of tJVF apart from a significant decrease in the PtPPA of tJVF, which can be attributed to the temporal characteristic of the tJVF pulsation. The diastolic phase was prolonged under the application of CPAP (see Fig. 3 and Table 3).

To further understand the results, we investigated the cerebral blood volume changes ( $\Delta CBV$ ) over the cardiac cycle according to Avezaat and van Eijndhoven [3].  $\Delta CBV(t)$  was analyzed according to Eq. (1) over the mean values of the flow rates with and without CPAP applied (Fig. 2).

$$\Delta CBV(t) = \int_0^t (tCBF(\tau) + k \cdot tJVF(\tau)) d\tau \quad (1)$$

Under the assumption that  $\Delta CBV(T) = 0$  over the duration  $T$  of the cardiac cycle, a scaling factor  $k$  was determined. Because only the jugular venous flow was recorded, parts of the venous cerebral outflow were missed, which was compensated by the scaling factor  $k$ . At Baseline,  $k$  was 1.15 and with CPAP,  $k$  was 1.08. Hence, on average the venous collateral outflow was underestimated by approximately 15% and 8%, respectively. The resulting maximum CBV changes at Baseline and under CPAP were 0.76 mL and 0.59 mL, respectively (Fig. 5). The maximum



**Fig. 4.** Juxtaposed frequency components (Hz) of normalized flow rates with CPAP (red, left) and at baseline (black, right) are illustrated using Box plots. In each panel, dotted lines separate the frequency components. In panel A, the first to the tenth frequency components of the tCBF are plotted. In panel B, the first to the seventh frequency components of the tJVF and in panel C, the first to the seventh frequency components of the CSF flow rate are illustrated. Curly brackets indicate significant differences of the respective frequency component's magnitudes analyzed with the Mann–Whitney U test.

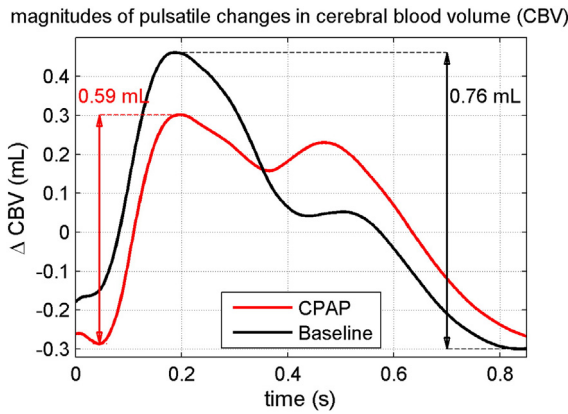
$\Delta CBV$  was therefore reduced under CPAP by approximately 23%. The decreased spinal CSF flow PtPPA and SV under CPAP can be accounted for the corresponding decreased maximum  $\Delta CBV$  as the spinal CSF flow pulsations are directly related to the spinal CSF volume displacements.

Using a different approach and considering intracranial pressure changes due to CPAP, in context of Marmarou's pressure–volume relation [1] Eq. (2), a decrease in cardiac-related volume displacements,  $\Delta V$ , would result in a decrease in ICP fluctuations; under the assumption that resting state ICP,  $P_{rest}$ , is equal with or without CPAP applied.

$$ICP = P_{rest} \cdot e^{0.1 \cdot \Delta V} \quad (2)$$

The assumption of constant ICP is supported by Muench et al. [38] who found that ICP was not impacted by positive end-expiratory pressure (PEEP) applied at 25 cmH<sub>2</sub>O in healthy pigs. In addition, Caricato et al. [39] and Georgiadis et al. [40] also found that ICP was not altered by PEEP application in patients with head injury and in acute stroke





**Fig. 5.** Average cerebral blood volume change ( $\Delta\text{CBV}(t)$ ) [3] with CPAP and at baseline computed based on the average arterial, venous and CSF flow waveforms for all subjects in the study. The maximum volume change with CPAP was 0.59 mL and at baseline was 0.76 mL. These alterations in CBV coincided with alterations in arterial inflow and venous outflow timing (Table 3). Under CPAP, the timing of the systolic maximum of tCBF was significantly later and the timing of the maximum caudal flow and local maximum of tJVF was significantly earlier, respectively.

patients, respectively. However, to our knowledge there are no studies in the literature that have quantified how CPAP administered via a full-face fitted mask may alter ICP in humans under healthy or pathological states. One can conjecture that if the pressure applied by CPAP propagates to the intracranial space it would alter CSF pressure dynamics in the spinal subarachnoid space. Increase in ICP would not necessarily increase spinal CSF flow pulsations because compliance in both compartments would decrease; this decrease could hinder CSF flow and result in a reduction in CSF flow amplitude. Our findings showed that CPAP significantly reduced CSF SV and PtPPA by 20% and 15%, respectively.

#### 4.3. Impact of CPAP on waveform features and timing

For the young adults in the present study (average age 24 years), the application of CPAP made their CSF and CBF waveform features similar to elderly people. The spinal CSF flow pattern under CPAP showed a behavior comparable to that reported in an earlier study we conducted on the physiological difference between age groups at the same location in the spine [21]. The diastolic timings and amplitudes of the elderly male volunteers reported in our previous study correspond to the current CPAP group results. The timing of the maximum caudal flow of the tJVF occurred earlier in the cardiac cycle under CPAP. This feature point did not correlate with the HR. The delay of tCBF systolic maximum under CPAP is possibly caused by the increase in the intrathoracic pressure accompanied by an increased resistance during the cardiac output. Most amplitudes of the spinal CSF flow feature points with CPAP differed significantly from those without.

The spectral content of the normalized tCBF only varies significantly in the fourth and the tenth frequency components. The effect of CPAP on the main arterial vessels of healthy young males appears therefore small. In the spinal canal, the fourth and the seventh frequency components of the CSF flow were significantly different with the presence of CPAP. The fundamental frequency of the tJVF was significantly decreased with CPAP, a finding that is related to the decreased tJVF PtPPA. Generally, the influence of CPAP appears to be more significant in the tJVF: the repeated measures ANOVA between the measurements with CPAP and those without were significantly different for the temporal locations of the respective feature points and the tJVF frequency content.

#### 4.4. Limitations

Using prospectively triggered image sequences, the acquisition window had to be set 10%–20% below the average cycle length. Therefore,

only 80%–90% of the entire cardiac cycle was covered and was available for data analysis. Due to the fact that no data were recorded for the remaining 10%–20% of the cardiac cycle, the diastolic phase is underestimated [46]. In the current study, we were only able to measure flow through the JVs since the structure and function of the overall cerebral venous system are difficult to assess with the current imaging techniques and as a result, there are only limited data published [47]. Thus, venous flow was approximated through the left and right JV. Furthermore, the venous system has primarily been studied in pathologic conditions such as cerebral venous thrombosis or multiple sclerosis [22]. Thus, there are no sufficient data to compare with the physiological states. We chose to adjust the CPAP level to 15 cmH<sub>2</sub>O in order to emphasize the maximum physiological effects of CPAP on vascular and CSF flow dynamics by minimizing possible bias. It is possible that this high pressure could have resulted in air-leaks and caused a gap between the applied and delivered mask pressure. However, the presence of air-leaks was repeatedly assessed during our MRI protocol by a medical doctor and adjusted when needed. Furthermore, all volunteers were asked to rate their anxiety level due to CPAP and 70% of the subjects tolerated the CPAP without any anxiety.

#### 5. Conclusion

Application of CPAP via a full-fitted mask at 15 cm H<sub>2</sub>O was found to have a significant effect on intracranial venous outflow and spinal CSF flow at the C2–C3 level in healthy awake adult volunteers. Intracranial arterial blood flow was not altered by CPAP and maintained consistent blood flow to the central nervous system tissue. These findings were attributed to the direct influence of CPAP on the intrathoracic pressure and not correlated with PtcCO<sub>2</sub> level reduction. CPAP is therefore a suitable non-invasive method to provoke changes in CBF and spinal CSF dynamics.

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